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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/688,904	10/21/2003	Gregory L. Kirk	11641/160	3770

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EXAMINER	
BOWERS, NATHAN ANDREW	
ART UNIT	**PAPER NUMBER**
1744	

DATE MAILED: 11/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/688,904	KIRK ET AL.	
	Examiner	Art Unit	
	Nathan A. Bowers	1744	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *082004, 061804*. 32 0604
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Objections

Claim 8 is objected to because of the following informalities: claim 8 includes the acronym TNF. It is necessary to write out the acronym TNF as tumor necrosis factor in the claims before use without an explanation. Appropriate correction is required.

Claim 16 is objected to because of the following informalities: claim 16 is currently dependent on claim 1. It is believed that claim 16 is intended to be dependent on claim 10. Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

1) Claims 1-5, 7 and 9 are rejected under 35 U.S.C. 102(a) as being anticipated by Jeon "Neutrophil chemotaxis in linear and complex gradients..."

With respect to claim 1, Jeon discloses a system for monitoring leukocyte migration. Jeon discloses a device that includes a housing defining a plurality of chambers. Each chamber includes a first well region and a second well region that are connected by a channel region. Additional inlets are provided for

introducing first and second substances to the fluidic system. In the "Results" and "Discussion" sections, Jeon states that different proportions of a chemoattractant are introduced to microchannels that split and recombine in order to produce a concentration gradient that is perpendicular to the flow of leukocytes. This is further illustrated in Figure 1.

With respect to claims 2 and 3, Jeon discloses the system in claim 1 wherein the first and second substances can either be the same or different. The system as described in considered to be fully capable of accommodating substances that are either the same or different.

With respect to claims 4 and 5, Jeon discloses the system in claim 1 wherein the first and second fluid streams converge into a third stream that comprises a concentration gradient of the first and second streams that is perpendicular to the direction of the flow of the third stream. The third stream then diverges into separate fourth, fifth and sixth streams, and then re-converges into a single seventh stream. This is described in the "Results" and "Discussion" sections, and is illustrated in Figure 1. Jeon emphasizes the use of laminar flow to ensure that the chemical gradient is stable by decreasing turbulent mixing.

With respect to claims 7 and 9, Jeon discloses the system in claim 1 wherein the first and second substances are cytokine test agents. Specifically, Jeon discloses the use of interleukin-8.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

2) Claims 1-3, 6, 7, 9 and 17-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harrison (US 6632619) in view of Jarnagin (US 6238874).

With respect to claim 1, Harrison discloses a system for the monitoring of leukocyte migration. Harrison discloses a first well (Figure 2:6), a second well (Figure 2:4), and a channel (Figure 2:2) that connects the first and second wells with one another. Harrison additionally teaches a first fluid stream (Figure 2:8') having a first concentration of a first substance, and a second fluid stream (Figure 2:8") having a second concentration of a second substance. The first and second fluid concentrations are different from one another and the first and second streams are in fluid communication with the chambers. This is described in column 2, line 38 to column 3, line 17, column 7, line 63 to column 9, line 4, and column 9, line 59 to column 10, line 46. Harrison, however, does not indicate that the system includes a plurality of chambers that each include a first well, second well, and connecting channel.

Jarnagin discloses a device for monitoring leukocyte migration comprising providing a housing including a plurality of chambers, wherein each chamber includes a first well region including at least one first well (Figure 5B:80), a second well region including at least one second well (Figure 5B:92), and a channel region including at least one channel (Figure 5B:94) connecting the first well region and the second well region with one another. Various motile cells are placed into the series of first wells, and chemotactic chemical agents are administered to the second well in order to induce movement of the cells across

the connecting channel. This is disclosed in column 10, line 50 to column 11, line 15. Jarnagin discloses that the invention is tailored to the analysis of leukocyte migration in column 15, lines 40-48 and in column 17, lines 1-6.

Harrison and Jarnagin are analogous art because they are from the same field of endeavor regarding chemotaxis devices.

At the time of the invention, it would have been obvious to modify the system proposed Harrison in order to provide a housing that comprises a plurality of first wells, second wells, and connecting channels. This would be beneficial because it would allow one to conduct numerous experiments simultaneously, thus improving efficiency. In column 8, lines 28-48 and lines 63-67, Jarnagin teaches that it is known in the art to construct chemotaxis systems so that chambers are disposed relative to one another to match a pitch of a standard microtiter plate containing any number of wells. This configuration would allow Harrison's system to correspond to established monitoring systems that have already been created for microtiter plate scanning.

With respect to claims 2 and 3, Harrison and Jarnagin disclose the apparatus set forth in claim 1 as set forth in the 35 U.S.C. 103 rejection above. Additionally, the system as described by Harrison in considered to be fully capable of accommodating substances that are either the same or different. In column 10, lines 36-46, Harrison teaches the use of multiple types of chemical substances.

With respect to claims 6, 7, 9 and 17, Harrison and Jarnagin disclose the apparatus set forth in claim 1 as set forth in the 35 U.S.C. 103 rejection above. Harrison additionally discloses a corresponding method in which the interaction between leukocytes and endothelial cells within the chamber are observed. In column 4, lines 40-45, column 5, lines 5-17, and column 20, line 29 to column 21, line 3, Harrison specifically discloses the presence of endothelial cells and various mediators such as selectins and cytokines. The selectins work as leukocyte capture mediators and leukocyte rolling mediators by reversibly binding to leukocytes and enabling them to roll across the endothelium. Harrison states that the cytokines inherently work by stopping leukocyte rolling, and causing leukocytes to flatten on the endothelium resulting in transmigration into the tissue. In column 8, lines 17-27, Harrison teaches that leukocyte rolling velocities are measured and analyzed.

With respect to claims 18 and 19, Harrison and Jarnagin disclose the method set forth in claim 17 as set forth in the 35 U.S.C. 103 rejection above. Harrison further discloses in column 6, line 66 to column 7, line 5 and in column 12, lines 45-52 the use of a video camera to view and detect leukocyte rolling at any given time and at predetermined intervals.

3) Claims 4 and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harrison (US 6632619) in view of Jarnagin (US 6238874) as applied to claim 1, and further in view of Jeon (US 6705357).

Harrison and Jarnagin disclose the apparatus set forth in claims 4 and 5 as set forth in the 35 U.S.C. 103 rejection above, however do not expressly disclose that the first and second fluid streams converge into a single third stream in order to produce a concentration gradient that is perpendicular to the direction of flow.

Jeon discloses an apparatus for combining and splitting different fluids in order to produce concentration gradients. First and second fluid streams converge into a single third fluid stream characterized by a concentration gradient that is substantially perpendicular to the direction of fluid flow. The third stream diverges into separate fourth, fifth, and sixth streams, and then re-converges into a single seventh stream. Jeon teaches that concentration gradients are formed under laminar flow. This is described in Figure 14, and in column 2, lines 7-33, column 4, line 25 to column 5, line 21, column 12, lines 5-23, and column 13, lines 41-51.

Harrison, Jarnagin and Jeon are analogous art because they are from the same field of endeavor regarding chemotaxis systems.

At the time of the invention, it would have been obvious to modify the fluidic circuit described by Harrison in order to create a system in which streams are combined into a common stream, split into a new set of separate streams, and then re-combined to produce a concentration gradient that is perpendicular to the direction of fluid flow. Jeon teaches in column 4, line 66 to column 5, line 21 that this is an effective way to create gradients for the study of chemotactic cells. Jeon further indicates that splitting and combining streams under laminar

flow conditions results in a device capable of attaining a steady state in which chemical concentrations at any position in the gradient are stable.

4) Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Harrison (US 6632619) in view of Jarnagin (US 6238874) as applied to claim 7, and further in view of Springer (US 5460945).

Harrison and Jarnagin disclose the apparatus set forth in claim 7 as set forth in the 35 U.S.C. 103 rejection above, however do not expressly disclose the use of TNF-α.

Springer discloses a device and method for the analysis of leukocyte migration and identification of inhibitors and promoters of the binding between leukocytes and endothelial cells. A variety of leukocyte migration mediators including selectins and integrins are provided in a sample chamber to facilitate binding reactions, and chemoattractants are used to ensure the proper movement to leukocytes towards the endothelium. See columns 10-15. Column 4, lines 20-29 and column 4, line 58 to column 5, line 21 state that TNF-α is known in the art as a cytokine that affects leukocyte migration.

Harrison, Jarnagin and Springer are analogous art because they are from the same field of endeavor regarding leukocyte migration observation systems.

At the time of the invention, it would have been obvious to introduce a plurality of different cytokines, such as TNF-α, in the apparatus disclosed by Harrison and Jarnagin. Springer indicates that TNF-α is useful in stimulating the activity of endothelial cells, and thereby promoting adhesion to leukocytes. In

this way, the introduction of TNF-α in Harrison's apparatus would have allowed one to observe leukocyte rolling and migration under a variety of conditions typical of biological environments.

5) Claims 10-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harrison (US 6632619) in view of Jeon (US 6705357).

With respect to claim 10, Harrison discloses the system as previously described in the rejections above. Harrison discloses an accompanying method in which migrating leukocytes are allowed to interact with endothelial cells disposed on a surface. In column 17, lines 47-59, it is indicated that fluids moving through the system are characterized by a laminar flow. Harrison, however, does not expressly state that the formed concentration gradients are perpendicular to the direction of flow.

Jeon discloses the system and method as previously described above. Fluid streams are combined and split in order to produce concentration gradients that are substantially perpendicular to the direction of fluid flow. Jeon teaches that concentration gradients are formed under laminar flow. This is described in Figure 14, and in column 2, lines 7-33, column 4, line 25 to column 5, line 21, column 12, lines 5-23, and column 13, lines 41-51.

Harrison and Jeon are analogous art because they are from the same field of endeavor regarding chemotaxis systems.

At the time of the invention, it would have been obvious to modify the fluidic circuit described by Harrison in order to create a system in which streams

are combined into a common stream, split into a new set of separate streams, and then re-combined to produce a concentration gradient that is perpendicular to the direction of fluid flow. Jeon teaches in column 4, line 66 to column 5, line 21 that this is an effective way to create gradients for the study of chemotactic cells. Jeon further indicates that splitting and combining streams under laminar flow conditions results in a device capable of attaining a steady state in which chemical concentrations at any position in the gradient are stable.

With respect to claims 11 and 12, Harrison and Jeon disclose the method set forth in claim 10 as set forth in the 35 U.S.C. 103 rejection above. In column 4, lines 40-45, column 5, lines 5-17, and column 20, line 29 to column 21, line 3, Harrison additionally discloses the presence of endothelial cells and various mediators such as selectins and cytokines. The selectins work as leukocyte capture mediators and leukocyte rolling mediators by reversibly binding to leukocytes and enabling them to roll across the endothelium. Harrison states that the cytokines inherently work by stopping leukocyte rolling, and causing leukocytes to flatten on the endothelium resulting in transmigration into the tissue.

With respect to claim 13, Harrison and Jeon disclose the method set forth in claim 10 as set forth in the 35 U.S.C. 103 rejection above. Harrison further discloses in column 4, lines 25-34 and column 7, lines 9-32 the use of a variety of pumping mechanisms capable of providing pulsatile flow conditions.

With respect to claims 14 and 15, Harrison and Jeon disclose the method set forth in claim 10 as set forth in the 35 U.S.C. 103 rejection above. Harrison additionally states in column 20, line 29 to column 21, line 3 that physiological shear flow along the surface is provided. Harrison also teaches that leukocyte rolling velocities are measured and analyzed.

With respect to claim 16, Harrison and Jeon disclose the method set forth in claim 10 as set forth in the 35 U.S.C. 103 rejection above. Harrison and Jeon both describe that the fluids are subjected to laminar flow conditions as they move through a microfluidic network of capillaries.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-7, 9-12 and 17 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 3-7 of copending Application No. 10/688905 in view of Harrison (US 6632619).

Application No. 10/688905 discloses a method of monitoring chemotaxis that involves the use of a plurality of chambers that each include a first well, second well, and connecting channel. Application No. 10/688905 further describes the introduction of a test substance and the formation of a gradient perpendicular to the flow of fluid. Application No. 10/688905 teaches the use of first and second streams that may be combined into a third stream, then split into fourth, fifth, and sixth streams, and finally re-combined into a seventh stream characterized by a gradient perpendicular to the fluid flow. Application No. 10/688905, however, does not indicate that the system is tailored to leukocyte migration or that endothelial cells are provided on the surface.

Harrison discloses the apparatus and method as previously described.

At the time of the invention, it would have been obvious to alter the method set forth in Application No. 10/688905 by disposing endothelial cells along the channel length as a means to encourage the study of leukocyte migration and rolling. Harrison teaches that this is an effective way to simulate and monitor the body's response to inflammation and injury.

This is a provisional obviousness-type double patenting rejection.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nathan A. Bowers whose telephone number is (571) 272-8613. The examiner can normally be reached on Monday-Friday 8 AM to 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gladys Corcoran can be reached on (571) 272-1214. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

NAB

GLADYS JP CORCORAN
SUPERVISORY PATENT EXAMINER